

REMARKS

Claims 1-11, 14-16, 18, and 20-34 are pending in the application. Claims 1, 14, 18, and 20 have been amended. Claims 12, 13, 17, and 19 have been cancelled without prejudice. Support for the amendments can be found in original claims 12, 13, 17, and 19 and in the specification at, e.g., page 2, line 11, to page 3, line 18. These amendments add no new matter.

Claim Objections

At page 2 of the Office Action, claim 17 was objected to as being of improper dependent form. Claim 17 has been cancelled without prejudice, thereby obviating this objection.

35 U.S.C. §101 (Non-Statutory Subject Matter)

At page 2 of the Office Action, claims 1-3 and 11 were rejected as being directed to non-statutory subject matter. Independent claim 1 has been amended to incorporate the limitations of original claims 12 and 13, which claims were not rejected under this heading. It is applicants' understanding that this amendment obviates the present rejection. As a result, applicants request that the Examiner withdraw the rejection of independent claim 1 and claims 2, 3, and 11 that depend directly or indirectly therefrom.

35 U.S.C. §102(b) (Anticipation)

At page 3 of the Office Action, claims 1-3, 9, 12, 18, 21, 22, 28, and 29 were rejected as allegedly anticipated by Gonzalez-Garcia et al. (1994) 120:3033-42 ("Gonzalez-Garcia").

Independent claim 1 has been amended to incorporate the limitations of original claim 13, which claim was not rejected under this heading. In addition, independent claim 18 has been amended to incorporate the limitations of original claim 19, which claim was not rejected under this heading. It is applicants' understanding that these amendments obviate the present rejection. As a result, applicants request that the Examiner withdraw the rejection of independent claims 1 and 18 and claims 2, 3, 9, 21, 22, 28, and 29 that depend directly or indirectly therefrom.

At page 4 of the Office Action, claims 1-3, 9, 11, 12, 18, 21, 22, 28, 29, and 30 were rejected as allegedly anticipated by Inohara et al. (1998) 273(15):8705-10 ("Inohara").

Independent claim 1 has been amended to incorporate the limitations of original claim 13, which claim was not rejected under this heading. In addition, independent claim 18 has been amended to incorporate the limitations of original claim 19, which claim was not rejected under this heading. It is applicants' understanding that these amendments obviate the present rejection. As a result, applicants request that the Examiner withdraw the rejection of independent claims 1 and 18 and claims 2, 3, 9, 11, 21, 22, 28, 29, and 30 that depend directly or indirectly therefrom.

35 U.S.C. §103(a) (Obviousness)

At pages 4-5 of the Office Action, claims 1, 4-7, and 10-12 were rejected as unpatentable over Goswami et al. (1999) 62:636-40 ("Goswami") in view of Gonzalez-Garcia.

Independent claim 1 has been amended to incorporate the limitations of original claim 13, which claim was not rejected under this heading. It is applicants' understanding that this amendment obviates the present rejection. As a result, applicants request that the Examiner withdraw the rejection of independent claim 1 and claims 4-7, 10, and 11 that depend directly or indirectly therefrom.

At pages 5-6 of the Office Action, claims 1-34 were rejected as unpatentable over Dixit et al., U.S. Patent No. 6,586,206 ("Dixit") in view of Goswami and further in view of Gonzalez-Garcia. According to the Office Action,

it would have been obvious to one of ordinary skill in the art at the time the instant invention as filed to recognize Bcl-XL and Bcl-2 are art-equivalents in term of function to extend viability of cells grown in cell culture especially in response to growth factor withdrawal. Therefore it would have been obvious to one of ordinary skill in the art to arrive at the claimed invention with a reasonable expectation of success by substituting Bcl-XL taught by Goswami et al. One of ordinary skill would have been motivated to arrive at the claimed invention given Pat. 6586206 teach that antibodies are well expressed in CHO cells and CHO cells viabilities are increased. Increased viability of antibody expressing cells would save time and cost associated with maintaining CHO cells.

Applicants respectfully traverse the rejection in view of the claim amendments and the following remarks.

Amended independent claim 1 is directed to a cell comprising an increased amount of bcl-xl protein, wherein the cell does not express a heterologous cyclin-dependent kinase inhibitor, wherein the cell further comprises a first expression vector encoding a polypeptide, wherein the polypeptide is a secreted protein, and wherein the cell produces an increased amount of the polypeptide as compared to a cell that does not comprise an increased amount of the bcl-xl protein. Amended independent claim 18 is directed to a method of producing a polypeptide in a cell comprising an increased amount of bcl-xl protein, wherein the cell does not express a heterologous cyclin-dependent kinase inhibitor, wherein the cell further comprises a first expression vector encoding a polypeptide, and wherein the cell produces an increased amount of the polypeptide as compared to a cell that does not comprise an increased amount of the bcl-xl protein.

Dixit describes methods of using apoptosis inhibitors to produce recombinant proteins in *in vitro* cell cultures. As detailed in Dixit, expression of the caspase-9 dominant negative apoptosis inhibitor in Chinese hamster ovary (CHO) cells increased resistance of the cells to apoptosis and prolonged cell viability. Dixit recites bcl-2 in the detailed description as one of several alternate apoptosis inhibitors that can be used in addition to the caspase-9 dominant negative protein. Dixit does not describe the use of bcl-xl as an apoptosis inhibitor that prolongs cell viability.

Goswami describes expression of bcl-2 in CHO cells as being able to extend cell viability, including in response to insulin and transferrin withdrawal. Like Dixit, Goswami also lacks description of expression of bcl-xl as extending cell viability.

Gonzalez-Garcia describes the cloning and characterization of the murine bcl-xl gene. As noted in the Office Action, Gonzalez-Garcia states that murine bcl-xl, like bcl-2, can act as a dominant inhibitor of cell death upon growth factor withdrawal.

In summary, Dixit and Goswami indicate that certain apoptosis inhibitors can be used to prolong cell viability and Gonzalez-Garcia identifies bcl-xl as an anti-apoptosis gene. However,

nothing in the cited references suggests an unexpected and highly advantageous feature that the inventors of the present application have found to be associated with increased expression of bcl-xl in a cell. As detailed in the specification, the inventors have made the unexpected discovery that when bcl-xl is expressed in a cell, that cell produces more protein (see specification at page 7, lines 12-14; page 17, lines 16-27; and Fig. 7B). The ability of bcl-xl expression to cause a significant increase protein production on a per cell basis (i.e., not simply through increased cell densities via inhibition of apoptosis) makes it particularly advantageous over other apoptosis inhibitors in recombinant protein production methods.

None of the cited references suggests that bcl-xl would have as a property the ability to increase the amount of protein produced by individual cells. There is no indication in the cited references that this property is shared by other apoptosis inhibitors such as caspase-9 dominant negative or bcl-2. Instead, the cited references merely indicate that certain apoptosis inhibitors prolong cell viability, which can lead to enhanced viable cell densities. As noted at MPEP 716.02(a), the

[p]resence of a property not possessed by the prior art is evidence of nonobviousness. *In re Papesch*, 315 F.2d 381, 137 USPQ 43 (CCPA 1963) (rejection of claims to compound structurally similar to the prior art compound was reversed because claimed compound unexpectedly possessed anti-inflammatory properties not possessed by the prior art compound); *Ex parte Thumm*, 132 USPQ 66 (Bd. App. 1961).

As summarized above, the ability of bcl-xl to increase protein production on a per cell basis is a significant unexpected result associated expression of bcl-xl in a cell. As a result, and contrary to the suggestion in the Office Action, bcl-2 and bcl-xl are not merely functional equivalents. Applicants respectfully submit that the presence of this unexpected property, which has not been described as being associated with other anti-apoptotic genes, is an objective indicia that establishes the nonobviousness of the currently claimed invention.

In view of the foregoing remarks, applicants request that the Examiner withdraw the rejection of independent claims 1 and 18 and the claims that depend directly or indirectly therefrom.

CONCLUSIONS

Applicants respectfully submit that all grounds for rejection have been overcome and that all claims are now in condition for allowance.

Enclosed is a Petition for Three Month Extension of Time. The extension of time fee is being paid concurrently herewith on the Electronic Filing System (EFS) by way of Deposit Account authorization. Please apply any other charges or credits to Deposit Account No. 06-1050, referencing Attorney Docket No. 13751-036US1.

Respectfully submitted,

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